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Bronchoscopic Lung Volume Reduction Coil Treatment for Severe Emphysema: A Systematic Review and Meta-Analysis of Individual Participant Data

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Keywords
Chronic obstructive pulmonary disease · Emphysema · Bronchoscopic lung volume reduction · Bronchoscopy · Meta-analysis

Abstract
Background: Lung volume reduction coil (LVR-coil) treatment provides a minimally invasive treatment option for severe emphysema patients which has been studied in multiple clinical trials. ***Objectives:*** The aim of the study was to assess the effect of LVR-coil treatment on pulmonary function, quality of life, and exercise capacity using individual participant data. ***Method:*** PubMed, Web of Science, and EMBASE were searched until May 17, 2021. Prospective single-arm and randomized controlled trials that evaluated the effect of LVR-coil treatment on forced expiratory volume in 1 s (FEV_1), residual volume (RV), St. George Respiratory Questionnaire (SGRQ) total score, and/or 6-min walk distance (6MWD) and were registered in an official clinical trial database were eligible for inclusion. Individual patient data were requested, and a linear mixed effects model was used to calculate overall treatment effects. ***Results:*** Eight trials were included in the final analysis, representing 680 individual patients. LVR-coil treatment resulted in a significant improvement in FEV1 at 3- (0.09 L [95% confidence interval (95% CI): 0.06–0.12]) and 6-month follow-up (0.07 L [95% CI: 0.03–0.10]), a significant reduction in RV at 3- (−0.45L [95% CI: −0.62 to −0.28]), 6- (−0.33L [95% CI: −0.52 to −0.14]), and 12-month follow-up (−0.36L [95% CI: −0.64 to −0.08]), a significant reduction in SGRQ total score at 3- (−12.3 points [95% CI: −15.8 to −8.8]), 6- (−10.1 points [95% CI: −12.8 to −7.3]), and 12-month follow-up (−9.8 points [95% CI: −15.0 to −4.7]) and a significant increase in 6MWD at 3-month follow-up (38 m [95% CI: 18–58]). ***Conclusions:*** LVR-coil treatment in emphysema patients results in sustained improvements in pulmonary function and quality of life and shorter lived improvements in exercise capacity. Since the owner of

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this LVR-coil has decided to stop the production and newer generations LVR-coils are currently being developed, these results can act as a reference for future studies and clinical guidance.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide [1]. The emphysema phenotype of COPD is characterized by destruction of lung parenchyma, which leads to a loss of elastic recoil and collapse of the small airways, resulting in air trapping and hyperinflation [2]. Patients with advanced emphysema and evident hyperinflation have limited effective treatment options. Effective treatments are surgical lung volume reduction and lung transplantation. However, these treatments are associated with a substantial morbidity risk and have limited availability, due to strict selection criteria, and the availability of lung transplantation is further limited by a shortage of donor organs [1].

Bronchoscopic lung volume reduction (BLVR) treatments are less invasive alternatives to surgery. Different BLVR devices have been developed to accommodate for the different phenotypes of emphysema [3]. Currently, one-way endobronchial valves are the most effective BLVR treatment option but require the absence of collateral ventilation [1, 3]. In contrast, endobronchial coils do not require the absence of collateral ventilation, extending BLVR options to a broader patient population.

Endobronchial coils are shape-memory nitinol (a nickel and titanium alloy) devices which are implanted in the sub-segmental airways under fluoroscopic guidance [4]. Preferably, coils are implanted bilaterally during two separate procedures, targeting the most destructed lobes [4]. A 2015 meta-analysis found significant improvements in pulmonary function, exercise capacity, and quality of life after lung volume reduction coil (LVR-coil) treatment based on the results of three single-arm and one, relatively small, randomized clinical trial (RCT) [5]. A 2019 meta-analysis also showed significant improvements in pulmonary function and quality of life after LVR-coil treatment, but no improvement in exercise capacity [3]. This 2019 meta-analysis only included RCTs and used aggregated data. A limitation to this strategy is that it ignores the results of single-arm trials which can lead to a substantial loss of information. Especially when a substantial part of all patients that received an experimental treatment is included in single-arm trials. Therefore, the aim of the current meta-analysis was to assess the effect of bronchoscopic LVR-coil treatment on pulmonary function, quality of life, and exercise capacity using individual participant data (IPD) of all registered clinical trials.

Methods

This systematic review and meta-analysis has been conducted in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) statement [6]. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020220306).

Search Strategy and Eligibility Criteria

A systematic literature search was conducted to identify RCTs and single-arm trials evaluating the efficacy of LVR-coil (RePneu, PneumRx/BTG Inc., Mountain View, CA, USA) treatment. Searches were conducted in PubMed, Web of Science, and EMBASE. The complete search strategy is described in the supplement. Searches were regularly updated until May 17, 2021. No language or date restrictions were included in the search. The following eligibility criteria were used at the study level: (1) prospective clinical trials, either RCT or single arm, that were (2) registered in an official clinical trial database, and (3) reported efficacy outcomes after LVR-coil treatment.

On a participant level, data were included up till 12 months after final LVR-coil treatment. Data of patients that did not form the original study population or that did not receive LVR-coil treatment despite allocation to the treatment group, was excluded. Furthermore, data of patients that were initially randomized to the "usual care" group and received LVR-coil treatment after crossover, was only included up till the point of crossover to the LVR-coil group.

Study Selection Process

The retrieved records were independently screened by two reviewers (S.A.R. and J.E.H.) in a two-step process. Firstly, the title and abstract of all retrieved records were screened and subsequently the full texts of the remaining records. Conflicts were resolved by discussion. If consensuses could not be reached a third reviewer (D.J.S.) was consulted.

Data Collection

For each eligible trial, IPD was requested from the principal investigator. If available, the following variables were extracted at all available time-points up till 12 months after final LVR-coil treatment: baseline patient characteristics, treatment allocation (for patients included in a RCT), pulmonary function test outcomes, 6-min walk distance (6MWD), St. George Respiratory Questionnaire (SGRQ) total score, and the number of the following serious adverse events (SAEs): pneumothorax, hemoptysis, acute COPD exacerbation, pneumonia, and death. Furthermore, procedure details were extracted for the patients who received LVR-coil treatment. No aggregated data were sought. The integrity of the supplied IPD was checked by attempting to replicate the

published results of baseline characteristics and the primary outcome. To the best of our ability, inconsistencies were resolved.

Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers (S.A.R. and J.E.H.). Discrepancies in judgement were resolved by discussion. The revised Cochrane Risk of Bias (RoB2) tool for randomized trials was used to assess the risk of bias in RCTs and the Risk of Bias in non-randomized Studies of Interventions (ROBINS-I) tool was used to assess risk of bias in single-arm trials.

Definition of Outcomes

The primary outcomes were estimated LVR-coil treatment effect on forced expiratory volume in 1 s (FEV_1), residual volume (RV), SGRQ total score, and 6MWD at 3, 6, and 12 months after final coil treatment. The secondary outcomes were responder rates (which were added in addition to the prospectively published protocol), procedure details, and the number of respiratory SAEs including mortality. Procedure details include procedure time, number and sizes of coils used, and location of coils per lung.

Data Synthesis and Statistical Analysis

Follow-up visits were defined as 3, 6, and 12 months after final LVR-coil treatment. If a different definition of follow-up was used in a trial, follow-up visits were adjusted (online suppl. Table 2; see www.karger.com/doi/10.1159/000524148 for all online suppl. material). Furthermore, if possible with the supplied data, predicted values for FEV_1 and RV were recalculated using the latest American Thoracic Society/European Respiratory Society guidelines [7, 8].

A one-stage approach was used to estimate the LVR-coil treatment effect on FEV_1, RV, SGRQ total score and 6MWD at 3-, 6-, and 12-month follow-up. This was done using a linear mixed effects model fit by the restricted maximum likelihood approach. Treatment arm (i.e., usual care or LVR-coil treatment) was fitted as a fixed effect and trial as random intercept to account for clustering of participants within trials. Trial was also fitted as a random slope but disregarded if the model failed to converge or if it did not lead to a significantly improved model. The upper and lower limits of 95% confidence intervals (95% CIs) were estimated using the bootstrap method with 2,000 bootstrap samples.

The responder rate in both LVR-coil and usual care group were calculated using the known MCIDs for FEV_1 (>+10%) [9], RV (<−0.31L) [10], SGRQ total score (<−4 points) [11], and 6MWD (>+26 m) [12]. *p* values were calculated using a χ^2 test. Procedure details are reported as descriptive statistics using frequency (percentage), mean (standard deviation), or median (range) as appropriate. SAEs are reported for both groups as frequency, risk ratio (95% CI), and *p* values. All statistical analysis was performed using R version 4.0.4 (2021-02-15) and the lme4 package version 1.1.26. Graphs were produced using the ggplot2 package version 3.3.3.

Results

Study Selection, Data Collection, and IPD Integrity

Nine trials were found eligible for inclusion, and all accepted to share IPD (shown in Fig. 1) [13–22]. One trial was unable to supply sufficient data to identify the original study population in the supplied IPD and was therefore excluded from the meta-analysis [20]. Therefore, a total of eight trials (four RCTs and four single-arm trials) were included in this meta-analysis. For these trials, the provided IPD was in accordance with the published aggregated data. Details on the record selection can be found in the supplement. Five trials reported outcomes at 3-month follow-up [14, 16, 18, 21, 22], four trials at 6-month follow-up [13, 15, 17, 19], and three trials at 12-month follow-up after final treatment [15, 17, 18] (shown in Fig. 1, and in online suppl. Table 2, 3).

Trial and Patient Characteristics

The inclusion and exclusion criteria were similar across all trials (online suppl. Table 4). The main trial and patient characteristics are shown in Table 1. Most variation between participant characteristics was seen in gender distribution, which ranged from 29% to 90% females across trials. Baseline characteristics were similar between the usual care and the LVR-coil treatment group, except for SGRQ total score, which was significantly lower in the usual care group (online suppl. Table 5).

Risk of Bias

Risk of bias for the RCTs ranged from some concerns to high. For the single arm studies, all trials were judged to have a moderate risk of bias (online suppl. Fig. 1).

Primary Outcome: LVR-Coil Treatment Effect

The results of the linear mixed effects models are shown in Figure 2 and in online supplementary Table 6. LVR-coil treatment led to a significant increase in FEV_1 at 3- and 6-month follow-up, a significant reduction in RV at 3-, 6-, and 12-month follow-up, a significant reduction in SGRQ total score at 3-, 6-, and 12-month follow-up, and a significant increase in 6MWD at 3-month follow-up compared to usual care. No significant effect of LVR-coil treatment was found in FEV_1 at 12-month follow-up and 6MWD at 6- and 12-month follow-up. Adjusting for the baseline imbalance in SGRQ total score, resulted in an estimated LVR-coil treatment effect of −10.9 (95% CI: −14.2 to −7.4) points, −9.5 (95% CI: −12.2 to −6.7), and −9.6 (95% CI: −14.8 to – 4.3) points at 3-, 6-, and 12-month follow-up, respectively.

Secondary Outcome: Responder Rate

The number of patients reaching the MCID for FEV_1, RV, SGRQ total score and 6MWD was significantly higher in the LVR-coil group at all follow-up timepoints, except for FEV_1 at 12-month follow-up (Table 2).

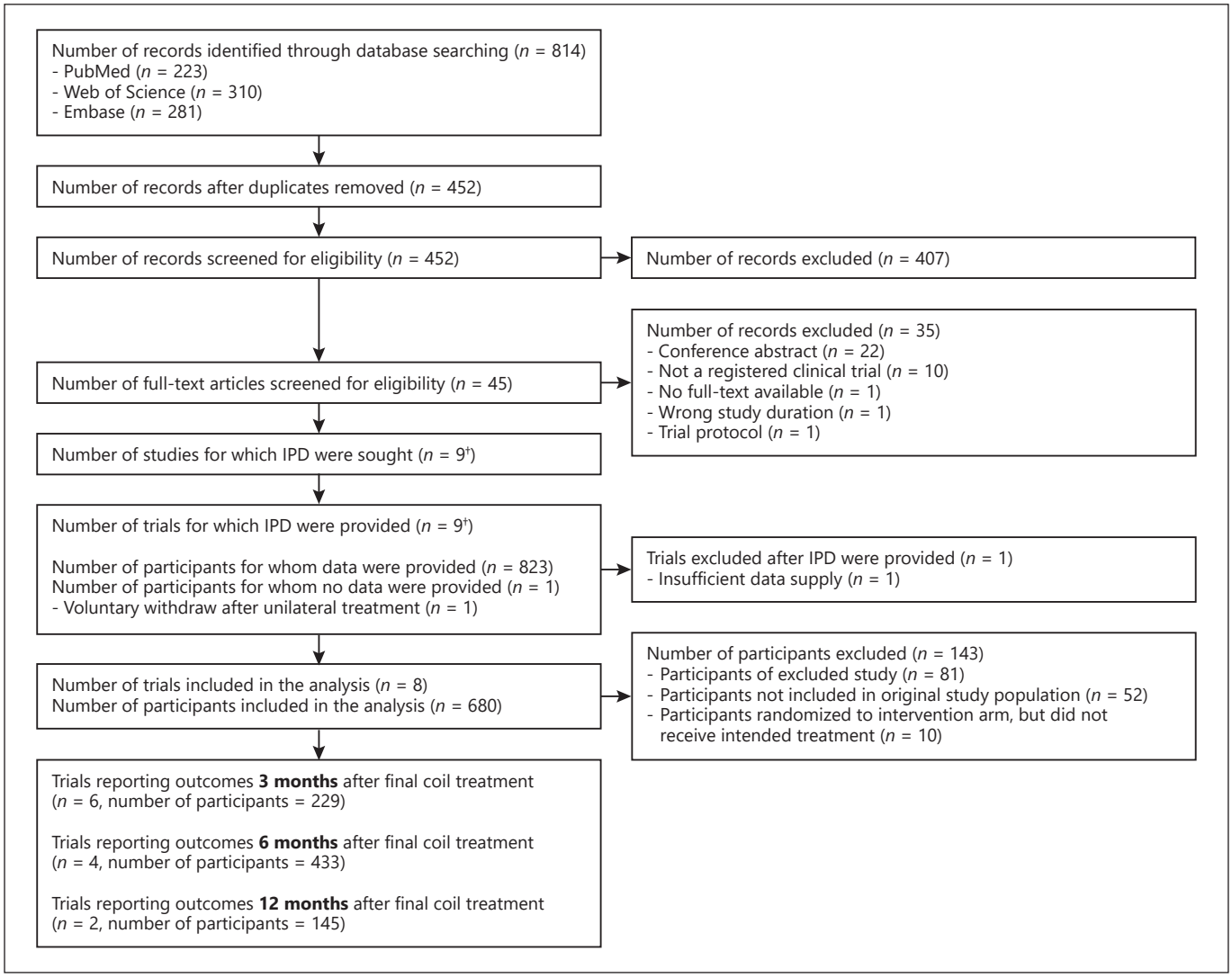

Fig. 1. Flow diagram of study selection. IPD, individual participant data. †10 records were included, of which 2 records reported on the same trial (RESET [14, 17]), and therefore IPD was sought for 9 trials.

Secondary Outcome: Procedure Details

In 411 patients, 788 LVR-coil procedures were performed (377 bilaterally and 34 unilaterally treated patients) with a median procedure time of 41 (15–140) minutes. Coil details were available for 651 procedures (83%), in which 6,639 coils were implanted with a median of 10 coils (range: 2–20) per procedure (online suppl. Table 7). LVR-coils were most frequently implanted in the upper lobes: 42% right upper lobe and 44% left upper lobe (online suppl. Fig. 2).

Secondary Outcome: SAEs

The risk of a serious respiratory adverse event was significantly higher in the LVR-coil treatment group compared to the usual care group, but no difference in risk of death between the groups was observered (Table 3).

Discussion

This systematic review and meta-analysis shows that bronchoscopic LVR-coil treatment in patients with advanced emphysema and evident hyperinflation leads to significant improvements in pulmonary function and quality of life up to 12 months after treatment, and a significant improvement in exercise capacity up to 3 months after

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Table 1. Trial and patient characteristics

	First author, year of publication (trial acronym)							
	Slebos et al. [13]	Shah et al. [14] and Zoumot et al. [17] (RESET)	Klooster et al. [16]	Deslée et al. [15]	Deslée et al. [18] (REVOLENS)	Sciurba et al. [19] (RENEW)	Hartman et al. [21] (REACTION)	Klooster et al. [22] (ELEVATE)
Trial registration No.	NCT01220908	NCT01334307	NCT01421082	NCT01328899	NCT01822795	NCT01608490	NCT02179125	NCT03360396
Study design	Single arm	RCT	Single arm	Single arm	RCT	RCT	Single arm	RCT
Sites, *n*	5	3	1	11	10	26	2	19
Site location(s)	Germany, The Netherlands	UK	The Netherlands	France, Germany, The Netherlands	France	Canada, France, Germany, The Netherlands, UK, US	The Netherlands, UK	Austria, France, Germany, Italy, The Netherlands, UK
Patients included in meta-analysis, *n*	16	45 (LVR-coil: 23, usual care: 22)	10	60	100 (LVR-coil: 50, usual care: 50)	312 (LVR-coil: 155, usual care: 157)	24	113 (LVR-coil: 73, usual care:40)
Emphysema distribution	Heterogeneous	Hetero- and homogeneous	Homogeneous	Heterogeneous	Hetero- and homogeneous	Heterogeneous	Hetero- and homogeneous	Hetero- and homogeneous
Gender (female)	12 (75)	18 (40)	9 (90)	33 (55)	29 (29)	163 (52)	17 (71)	59 (52)
Age, years	57 (8)	63 (8)	56 (7)	60 (7)	62 (8)	64 (8)	62 (7)	63 (7)
FEV_1 (predicted, %)	26 (6)	27 (8)	22 (4)	28 (6)	24 (6)	26 (6)	24 (7)	27 (6)
RV (predicted, %)	225 (43)	226 (51)	270 (49)	248 (54)	271 (41)	245 (39)	231 (38)	251 (40)
RV/TLC (ratio)	60 (6)	62 (7)	68 (4)	66 (8)	70 (7)	67 (6)	63 (6)	67 (6)
SGRQ (total score)	62 (13)	58 (13)	59 (10)	61 (14)	59 (14)	59 (14)	56 (10)	57 (13)
Follow-up visits	6 months after final treatment	6 + 12 months after final treatment	6 months after first treatment	6 + 12 months after final treatment	6 + 12 months after randomization	12 months after first treatment	3 months after final treatment	6 months after first treatment
Funding	PneumRx, Inc.	PneumRx, Inc.	PneumRx, Inc.	PneumRx, Inc.	French ministry of health	PneumRx/BTG, Inc.	Investigator initiated trial	PneumRx/BTG, Inc. & Boston scientific corporation

Data are presented as *n* (%) or mean (SD). RCT, randomized controlled trial; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; SGRQ, St. George respiratory questionnaire.

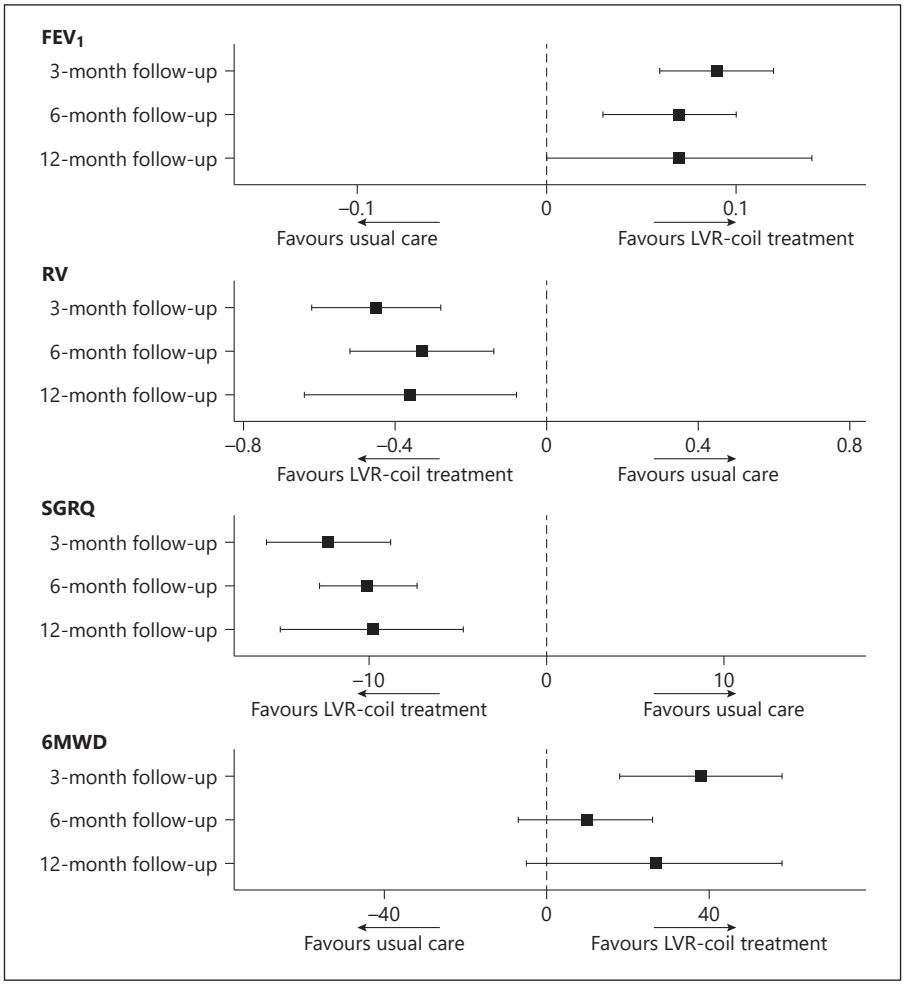

Fig. 2. Mixed effect model estimates of coil treatment including 95% CI. FEV1, forced expiratory volume in 1 s; RV, residual volume; SGRQ, St. George respiratory questionnaire; 6MWD, 6-min walk distance.

treatment. These treatment effects came at a cost of an increased risk of serious respiratory adverse events compared to usual care, but not with an increased risk of death.

BLVR options for patients who do not qualify for one-way endobronchial valve treatment or lung volume reduction surgery, i.e., patients with predominant homogeneous emphysema and/or collateral ventilation, are still limited. LVR-coil treatment provides a treatment option for this patient population. This meta-analysis shows promising results for improvements in quality of life by reductions in SGRQ total score that reach the MCID of 4 points up till 12 months after treatment [11]. However, in none of the included trials, patients were blinded for their treatment allocation. This may potentially lead to the introduction of a placebo effect, resulting in an overestimation of the positive treatment effect. Nevertheless, the clinical meaningful improvement in quality of life persists up till 12 months after treatment, suggesting that this finding might be a true effect rather than a placebo effect. Furthermore, the EASE trial, a double-blind, randomized, sham-controlled clinical trial, comparing airway bypass against usual care found only a minor placebo effect on SGRQ total score [23]. The reduction in SGRQ total score is also accompanied by a sustained and significant improvement in pulmonary function with a reduction in RV that reaches the MCID of −0.31 L up till 12 months after treatment and an increase in FEV_1 that reaches statistical significance up till 6 months after treatment and reaches the MCID of +10% up till 12 months after treatment.

In contrast to the sustained improvements in pulmonary function and quality of life, 6MWD only showed a significant improvement till 3 months after LVR-coil treatment. A previous post-hoc study found improvement in quality of life and absence of cardiac disease to be independent predictors for improvements in exercise capacity after LVR-coil treatment [24]. Comorbidity data were not included in this meta-analysis but might be a reason for the only short-lived improvement. Neverthe-

Table 2. Number of patients who reached the minimal clinically important difference

	3-month follow-up			6-month follow-up			12-month		
	LVR-coil, *n* (%)	usual care, *n* (%)	*p* value	LVR-coil, *n* (%)	usual care, *n* (%)	*p* value	LVR-coil, *n* (%)	usual care, *n* (%)	*p* value
Δ FEV_1 >10%	80 (50)	15 (14)	<0.001	95 (42)	22 (16)	<0.001	32 (33)	8 (17)	0.07
Δ RV <–0.31L	100 (64)	29 (28)	<0.001	121 (53)	38 (27)	<0.001	54 (57)	12 (26)	0.001
Δ SGRQ total score <–4 points	103 (66)	27 (26)	<0.001	144 (62)	42 (30)	<0.001	56 (59)	15 (33)	0.01
Δ 6MWD >26 m	51 (52)	17 (26)	0.001	104 (45)	35 (25)	<0.001	41 (43)	9 (20)	0.02

LVR, lung volume reduction; FEV_1, forced expiratory volume in 1 s; RV, residual volume; SGRQ, St. George respiratory questionnaire; 6MWD, 6-min walk distance.

Table 3. Respiratory SAEs and deaths across LVR-coil treatment and usual care group

	LVR-coil treatment (*n* = 298)		Usual care (*n* = 229)		RR (95% CI)	*p* value
	events	patients, *n* (%)	events	patients, *n* (%)		
Pneumothorax	31	30 (10)	8	7 (3)	3.3 (1.5–7.4)	0.002
Haemoptysis	6	6 (2)	0	0 (0)	–	–
COPD exacerbation	135	92 (31)	69	49 (21)	1.4 (1.1–1.9)	0.01
Pneumonia	69	62 (21)	17	13 (6)	3.7 (2.1–6.5)	<0.001
Death	15	15 (5)	16	16 (7)	0.7 (0.4–1.4)	0.34

Data of the ELEVATE were not included because only data on death were available. LVR, lung volume reduction; RR, relative risk; 95% CI, 95% confidence interval.

less, the number of patients reaching the MCID for 6MWD stays relatively stable around 45% in the LVR-coil group up till 12 months after treatment, and the responder rate is significantly higher compared to the usual care group. The improvements associated with LVR-coil treatment are accompanied by a significant increase in respiratory SAEs compared to usual care but not with a higher risk of death. Previous studies have shown that the rate of SAEs decreases with time after LVR-coil treatment which could not be tested in this meta-analysis because time between treatment and the occurrence of SAE was not known for all patients included [5, 25].

Targeting the most destructed lobes by emphysema is one of the most important predictors for LVR-coil treatment success [26]. In all trials included in this meta-analysis, except the ELEVATE trial, selection of target lobes was based upon visual inspection of the chest CT-scan. A previous study has shown that the interobserver agreement for selecting the most destructed lobes was only fair to moderate and that disagreements were more common for patients with a more homogeneous distribution of emphysema [27]. Furthermore, a post hoc analysis of the RENEW trial has shown that one-third of the patients with a homogeneous distribution of emphysema was not treated in the most destructed lobes as identified by quantitative CT (QCT) analysis [26]. This could have negatively affected the average effect of LVR-coil treatment in this meta-analysis. Unfortunately, we did not have emphysema distribution data available for all trials and therefore were not able to perform sub-analysis to confirm this. For future LVR-coil-studies, it is important to take this into consideration in the patient and target lobe selection process.

Including QCT analysis might improve the overall LVR-coil treatment effect by improving target lobe selection. The ELEVATE trial is the last conducted RCT comparing LVR-coil treatment with usual care and the only trial that included QCT for target lobe selection [18]. The results of this trial are comparable to the overall treatment effect found in this meta-analysis. However, this trial was prematurely terminated by the study sponsor (Boston Scientific Corporation, Marlborough, MA, USA), the latest owner of the LVR-coils. This decision by the study

sponsor was soley based on business reasons. The ELEVATE trial was terminated after 57% of the intended number of patients were included. Therefore, it cannot be concluded if adding QCT leads to an improvement in overall treatment effect. Furthermore, no data on 6MWD were available for this trial. The decision of the sponsor to discontinue the production of the LVR-coils, led to the design and production of new LVR-coil versions, currently under investigation in several clinical trials (NCT04520152 and NCT03685526). Therefore, this meta-analysis gives an estimate of the overall treatment effect based on all clinical trials that will ever be performed using this type of LVR-coil, and the results of this meta-analysis can be used as a comparator for the results of the new generation LVR-coils.

The main strength of this meta-analysis is that it was conducted using individual patient data from all studies that will be performed with this kind of LVR-coil and which have assessed equal outcomes measures with similar in- and exclusion criteria. The use of a mixed model allowed for determining an overall treatment effect also including single-arm studies with correction for participant clustering within trials. Furthermore, follow-up time was adjusted based on time after last treatment further equalizing the included trials and their results.

However, this study also has some limitations. Firstly, in none of the studies, patients were blinded and none of the RCTs were sham controlled. This might have biased the outcomes, especially quality of life, although it is expected that this effect is small. Furthermore, a sham-controlled trial is very difficult for a treatment with radiographically visible implants, which can easily result in accidental unblinding. Secondly, data on emphysema distribution per patient were not available for all patients. Therefore, no sub-analysis could be done to test for differences in treatment effect between patients with a homogeneous and heterogeneous emphysema distribution or between patients who were treated in the most destructed target lobe or not. However, a previous LVR-coil meta-analysis has found no difference in treatment effect between patients with homogeneous and heterogeneous emphysema [5]. Lastly, in this meta-analysis, the estimated treatment effect was determined at 3-, 6-, and 12-months after final coil treatment. Although this gives a better estimate than combining the primary endpoint results of all trials, this led to only having usual care group from one trial at 6- and 12-month follow-up (RENEW and REVOLENS, respectively).

In conclusion, this meta-analysis shows that LVR-coil treatment is an effective treatment for patients with severe emphysema and evident hyperinflation and results in long-term improvements in quality of life and pulmonary function, and shorter lived improvements in exercise capacity at a risk of increased respiratory adverse events but not an increased mortality risk. However, there is room for improvement as only around half of treated patients reach at least one of the MCIDs (FEV_1, RV, SGRQ total score and 6MWD). It is to note that to achieve these results and minimize the adverse events rate, a high level of competence is required from the physician performing the procedure and it should therefore be performed only in specialized centers by trained physicians. The results of this meta-analysis will be of interest for future studies with newly designed LVR-coils (e.g., NCT04520152 and NCT03685526) and could be used as a reference. Furthermore, including quantitative CT analysis and more hyperinflation parameters, such as inspiratory capacity to total lung capacity, into these new trials might give additional insight into the effect of LVR-coil treatment.

Statement of Ethics

This is a systematic review and meta-analysis with studies acting as the unit of analysis instead of patients. As such, written consent and ethics approval were not required. The included studies were all approved by the local Ethics Committee, and all included patients supplied written informed consent. This systematic review and meta-analysis complied with the reporting guidelines established by PRISMA to ensure transparency, and the study protocol was prospectively registered into PROSPERO with the reference ID: CRD42020220306.

Conflict of Interest Statement

Gaëtan Deslée reported grants or contracts and consulting fees from BTG/PneumRx Inc. outside the current study. Felix Herth reported grants or contracts from PulmonX Corp., Bronchus medical Inc. and Olympus Corp., Tokio, Japan, and consulting fees from AstraZeneca, CSL Behring, and lecture fees from GlaxoSmithKline, Chiesi pharmaceuticals B.V. and Streamedup, and participation on a DSMB or advisory board for Apogenix, outside of the current study. Karin Klooster has reported lecture fees from PulmonX and Chiesi pharmaceuticals B.V., outside of the current study. Frank Sciurba reported grants or contracts from Gala Therapeutics, PulmonX Corp. and Nuvaira, Inc., outside the current study. Zaid Zoumot reported registration fees and travel costs for attending the ATS 2013 and the ACCP congress Atlanta 2012 meeting, outside of the current study. Dirk-Jan Slebos reported grants or contracts, registration fees and travel costs and participation on the DSMB from PulmonX, Corp. and BTG/PneumRx Inc., outside the current study. The other authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study concept and design. S.A.R. and J.E.H. performed the study search, study selection, and risk of bias assessment. S.A.R. was responsible for data acquisition of the IPD, performed the statistical analysis, and wrote the manuscript. J.E.H. supervised statistical analysis and critically reviewed the manuscript. D.J.S. supervised the project, supported in data acquisition and critical review of the manuscript. All other authors provided the original individual patient data and contributed to the critical review of the manuscript.

Data Availability Statement

Data are available upon reasonable request.

References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2021 report. https: //goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf2021.
2 Kemp SV, Polkey MI, Shah PL. The epidemiology, etiology, clinical features, and natural history of emphysema. Thorac Surg Clin. 2009 May;19(2):149–58.
3 van Geffen WH, Slebos DJ, Herth FJ, Kemp SV, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. Lancet Respir Med. 2019 Apr;7(4):313–24.
4 Slebos DJ, Ten Hacken NH, Hetzel M, Herth FJF, Shah PL. Endobronchial coils for endoscopic lung volume reduction: best practice recommendations from an expert panel. Respiration. 2018;96(1):1–11.
5 Slebos DJ, Hartman JE, Klooster K, Blaas S, Deslee G, Gesierich W, et al. Bronchoscopic coil Treatment for patients with severe emphysema: a meta-analysis. Respiration. 2015;90(2):136–45.
6 Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015 Apr 28;313(16):1657–65.
7 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. [Lung volumes and forced ventilatory flows. Work group on standardization of respiratory function tests. European community for coal and steel. official position of the european respiratory society]. Rev Mal Respir. 1993 Mar;16:5–40.
8 Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official american thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70–e88.
9 Donohue JF. Minimal clinically important differences in COPD lung function. COPD. 2005;2(1):111–24.
10 Hartman JE, Ten Hacken NH, Klooster K, Boezen HM, de Greef MH, Slebos DJ. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J. 2012 Nov;40(5):1137–41.
11 Jones PW. St. George's respiratory questionnaire: MCID. Copd. 2005 Mar;2(1):75–9.
12 Puhan MA, Chandra D, Mosenifar Z, Ries A, Make B, Hansel NN, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J. 2011 Apr;37(4):784–90.
13 Slebos DJ, Klooster K, Ernst A, Herth FJF, Kerstjens HAM. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest. 2012 Sep;142(3):574–82.
14 Shah PL, Zoumot Z, Singh S, Bicknell SR, Ross ET, Quiring J, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. Lancet Respir Med. 2013 May;1(3):233–40.
15 Deslee G, Klooster K, Hetzel M, Stanzel F, Kessler R, Marquette CH, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax. 2014 Nov;69(11):980–6.
16 Klooster K, Ten Hacken NH, Franz I, Kerstjens HA, van Rikxoort EM, Slebos DJ. Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: a prospective feasibility trial. Respiration. 2014;88(2):116–25.
17 Zoumot Z, Kemp SV, Singh S, Bicknell SR, McNulty WH, Hopkinson NS, et al. Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial. PLoS One. 2015;10(4):e0122656.
18 Deslee G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, et al. Lung volume reduction coil treatment vs usual care in patients with severe emphysema: the REVOLENS randomized clinical trial. JAMA. 2016 Jan 12;315(2):175–84.
19 Sciurba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, et al. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. JAMA. 2016 May 24–31;315(20):2178–89.
20 Fellrath JM, Scherer T, Franzen DP, Lovis A, von Garnier C, Plojoux J, et al. Endobronchial coil therapy in severe emphysema: 6-month outcomes from a Swiss National Registry. J Thorac Dis. 2018 Aug;10(Suppl 23):S2711–18.
21 Hartman JE, Klooster K, Augustijn SWS, van Geffen WH, Garner JL, Shah PL, et al. Identifying responders and exploring mechanisms of action of the endobronchial coil treatment for emphysema. Respiration. 2021;100(5):443–51.
22 Klooster K, Valipour A, Marquette CH, Boutros J, Mal H, Marceau A, et al. Endobronchial coil system versus standard-of-care medical management in the treatment of subjects with severe emphysema. Respiration. 2021 May 7;100:804–10.
23 Shah PL, Slebos DJ, Cardoso PF, Cetti E, Voelker K, Levine B, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Lancet. 2011 Sep 10;378(9795):997–1005.
24 Hartman JE, Shah PL, Sciurba F, Herth FJF, Slebos DJ, Group RS. Endobronchial coils for emphysema: dual mechanism of action on lobar residual volume reduction. Respirology. 2020 Nov;25(11):1160–6.
25 Hartman JE, Klooster K, Gortzak K, Hacken NHT, Slebos DJ. Long term follow up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema. Respirology. 2015;20(2):319–26.
26 Slebos DJ, Cicenia J, Sciurba FC, Criner GJ, Hartman JE, Garner J, et al. Predictors of response to endobronchial coil therapy in patients with advanced emphysema. Chest. 2019 May;155(5):928–37.
27 Hartman JE, Criner GJ, Moore WH, van Rikxoort EM, Sciurba FC, Shah PL, et al. HRCT characteristics of severe emphysema patients: interobserver variability among expert readers and comparison with quantitative software. Eur J Radiol. 2021 Mar;136:109561.